REMARKS

Independent Claims 1, 6, and 11 have been amended to remove the statement that the binding site has "known geometry" and to further clarify that the "plurality" in the determining step or means refers to a plurality of common core positions. Claims 1, 6, and 11 have also been amended to clarify that the clusters are clusters of ligands from the plurality of ligands. The Applicant respectfully submits that this meaning was apparent from the previous claim language but have made the amendment to remove any possible ambiguity. The Applicant respectfully submits that this amendment is not being made for a reason related to patentability. Support for this amendment may be found, for example, in the specification at paragraphs 20, 66, and 87. Claims 1, 6, and 11 have also been amended by adding method or means limitations for rating complementarity of the combinatorial library to the target molecule based on the clusters formed. This amendment finds support, for example, in original Claims 2, 7, and 12, respectively, and in the specification at paragraphs 20, 66, and 87-91. Dependent claims 2, 7, and 12 have been amended to make them consistent with the added limitations to Claims 1, 6, and 11. Finally, Claims 1-3, 6-8, and 11-13 have been amended to specify that the abbreviation "rms" refers to root mean square.

Claims 1-15 remain pending in the application. The Applicant has carefully considered all of the Examiner's rejections but respectfully submits that the pending claims are allowable for at least the reasons presented below.

Rejections under § 112 – Indefiniteness

The Examiner rejected Claims 1-15 under 35 U.S.C. § 112, ¶ 2 as being indefinite. The Examiner asserted that the abbreviation "rms" in the claims is vague and indefinite unless accompanied by the full name in parentheses. As noted above, the Applicant has herein amended the claims to specify "rms (root mean square)" where the abbreviation "rms" appears. The Examiner also asserted that it was unclear what the limitation "said plurality" in the determining step or means of Claims 1, 6, and 11 referred to. The Applicant has herein amended the claims to clarify that "said plurality" refers to the plurality of common core positions. Accordingly, the Applicant has responded to the Examiner's concerns and respectfully submits that the rejections have been overcome.

Rejections under § 112 – Written Description

The Examiner rejected Claims 1-15 under 35 U.S.C. § 112, ¶ 1 as failing to comply with the written description requirement. The Examiner asserted that the limitation of "binding site of known geometry" is not supported by the specification and thus, constitutes new matter. The Applicant has herein removed the statement "of known geometry" thereby obviating the Examiner's rejections.

Rejections under § 103

The Examiner rejected Claims 1, 2, 5, 6, 7, 10-12, and 15 under 35 U.S.C. § 103(a) as being unpatentable over Ho et al. (1994) taken with Rarey et al. (1996). The Examiner asserted that Ho discloses a method and system for searching for complementary components in a chemical library and that Rarey discloses ranking of ligands based on rms deviations. The Examiner argued that one could improve on Ho by using the ranking of ligands based on rms deviations taught by Rarey.

The Applicant respectfully submits that the instant claims are not obvious over Rarey and Ho. Independent Claims 1, 6, and 11 are directed to rating the complementarity of an ***entire combinatorial library*** to a target molecule. In contrast, Rarey is directed to docking a ***single molecular fragment*** to the active site of a receptor. For example, when Rarey discusses clustering, it is in reference to clustering of different placements of a single fragment. Ho is directed to generating novel ligands.

Rarey et al. discloses an algorithm for placing molecular fragments into the active site of a receptor. *See* page 41, summary. A given molecular fragment is placed into the active site using a plurality of transformations. RMS deviations between different placements of the fragment are used as a distance measure for clustering the plurality of transformations. *See* page 46, column 2. The success of different placements, or clusters of placements, was tested for various ligands and evaluated using rms deviation from the known crystal structure and comparison of estimated and experimentally observed binding energies. *See* page 49, Table 5 and page 50, column 2.

Ho et al. discloses a drug design system. *See* page 213, summary. The system first generates a model of an active site. *See* page 214, column 2 to page 215, column 2. Databases of

3D components for matching with the active site model can be constructed. *See* page 215, column 2. Molecular fragments complementary to the active site are retrieved and docked in the active site. *See* page 216, column 1. The molecular fragments are then edited by clipping off fragments to ensure steric fit. *See* page 216, column 1. Finally, novel ligands are built by assembling the molecular fragments. *See* page 217, column 1.

A *prima facie* case of obviousness requires that all of the claim limitations are taught or suggested by the prior art. *See* M.P.E.P. § 2143.03. Claim 1 requires the steps of determining rms deviation of one or more common core positions from one or more other common core positions, forming clusters of ligands according to the rms deviation, and rating the complementarity of the combinatorial library based on the clusters formed. Similarly, Claim 6 requires a system comprising means corresponding to the above steps and Claim 11 requires a program storage device, tangibly embodying a program of instructions corresponding to the above steps.

Neither Rarey nor Ho disclose or suggest the claimed limitation of determining the rms deviation of one or more common core positions over different ligands from one or more ***other*** common core positions. Rarey only discloses rms deviations between different transformations of the ***same*** fragment (page 46, column 2) or rms deviations between a fragment and a crystal structure (page 50, column 1). Notably, the rms deviations listed in Table 5 are deviations between a particular fragment transformation and the actual position determined by crystal structure. They are not deviations between different dockings. Ho does not even mention rms deviations.

Finally, neither Rarey nor Ho disclose or suggest the claimed limitation of rating complementarity of a ***combinatorial library*** to a target molecule based on clusters. Rarey and Ho say nothing about rating a combinatorial library comprising a ***plurality*** of ligands having a common core. Rarey only discusses the success of binding predictions of ***independent*** ligands (e.g., the nine individual ligands presented in Table 5). Ho only discusses designing novel ligands. The ligands constructed by Ho are not even part of a database (e.g., multiple components from a database are fit within an active site and then edited and assembled to construct ***novel*** ligands, *see* page 216, column 2 to page 217, column 1). Thus, the claimed step of rating the complementarity of a combinatorial library to a target molecule is not suggested by

either Rarey or Ho. Accordingly, the Applicant respectfully submits that there cannot be a *prima facie* case of obviousness of independent Claims 1, 6, and 11 over Rarey and Ho. Similarly, all claims depending from Claims 1, 6, and 11 are allowable.

The Examiner also rejected Claims 1-3, 5-8, 10-13, and 15 under 35 U.S.C. § 103(a) as being unpatentable over Ho et al. taken with Rarey et al. in view of DeLisi et al. (1996). The Examiner asserted that DeLisi discloses using a grid for determining rms deviations. The Examiner does not argue that DeLisi discloses or suggests any of the limitations of Claims 1, 6, and 11 that are lacking in Rarey and Ho. Accordingly, the Applicant respectfully submits that for at least the same reasons as discussed above, Claims 1-3, 5-8, 10-13, and 15 are allowable over Ho et al. taken with Rarey et al. in view of DeLisi et al.

The Examiner also rejected Claims 1, 2, 4-7, 9-12, and 14-15 under 35 U.S.C. § 103(a) as being unpatentable over Ho et al. taken with Rarey et al. in view of Aldenderfer et al. (1984). The Examiner asserted that Aldenderfer discloses a single-linkage clustering algorithm. As with DeLisi, Aldenderfer does not disclose or suggest any of the limitations of Claims 1, 6, and 11 that are lacking in Rarey and Ho. Accordingly, the Applicant respectfully submits that for at least the same reasons as discussed above, Claims 1, 2, 4-7, 9-12, and 14-15 are allowable over Ho et al. taken with Rarey et al. in view of Aldenderfer et al.

CONCLUSION

The Applicant respectfully submits that the pending claims are in condition for allowance and requests the timely issuance of a Notice of Allowance.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,
KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 10/21/04

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